# STATISTICS, RISK MANAGEMENT AND CLINICAL TRIAL DESIGN

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# QUANTITATIVE METHODS

- Clinical trial design and analysis
- Quality control assessment
- Post-marketing surveillance
- Pharmacogenomics
- Risk analysis

# QUANTITATIVE METHODS AND CRITICAL PATH

- Maximizing efficiency while maintaining reliability
  - Improved analytical approaches
  - Flexible study designs
- Transparency
  - Best practices
  - Underlying assumptions

# CBER-SPECIFIC ISSUES

- Many topics are relevant to product issues in all Centers
- Some topics are of particular relevance to biologics
- Some areas may need to be handled somewhat differently for biologics

# CBER PRODUCTS

- Vaccines
  - Huge target populations
  - Administered to healthy people
  - Major public health impact
  - Growing public concerns re safety
- Blood, blood products and tissues
  - Life-saving therapies
  - Potential to transmit serious disease
- Cellular and gene therapies
  - Emerging approaches
  - Potential for great benefit, high risk
  - Target populations may be small

# STUDY ENDPOINTS

- Biomarkers
- Intermediate endpoints
- Composite endpoints
- Multiple endpoints
- Assessment scales

# BIOMARKERS AND SURROGATE ENDPOINTS

- Great potential for speeding product development
- Documented success in many areas
  - Vaccines
  - HIV
  - Cardiovascular disease prevention
- But also: documented potential to mislead

# BIOMARKERS AND SURROGATE ENDPOINTS

- Infectious disease processes often well understood, perhaps more so than those of many chronic diseases
- In vaccine development, immune response well accepted as surrogate for disease protection in many cases
- Emerging technologies that enhance understanding of disease processes may pave way for increased reliance on biomarkers/surrogates

# CONSTRUCTING/SELECTING ENDPOINTS

- Statistical considerations needed for identification and evaluation of efficient and reliable endpoints
- Recent CBER investigations:
  - Renal transplantation: Can we identify surrogates for long-term graft survival to avoid renal biopsy?
  - Myositis: Constructing clinical assessment scales

# GENOMICS/PROTEOMICS

- Rapidly emerging area throughout FDA
- Statistical practices not well established for microarray data
- Staff training a high priority
- Current project: evaluation of statistical approaches and software packages

# STATISTICS IN MANUFACTURING

- Quality control in blood collection
  - Low volume processing
  - False positives highly burdensome
  - Alternative statistical approaches may improve efficiency
- Vaccine lot consistency
  - Methods developed for cases where normal distribution of variables cannot be assumed

# FLEXIBLE STUDY DESIGN

- Initial parameters may be inaccurate
- Interim modification may improve trial ability to answer question
- Traditional approaches
  - Group sequential designs with early stopping for efficacy, harm, futility
  - Other changes acceptable if not influenced by knowledge of interim data
- Emerging approaches

# FLEXIBLE STUDY DESIGN

- New designs permit even greater flexibility
- Some debate about actual efficiency of such designs
- CBER sponsoring joint workshop (with Harvard-MIT Division of Health Science Technology) on potential for such designs in drug development

# FLEXIBLE DESIGNS FOR BIOLOGICS

- CBER regulates cutting-edge products
  - Cellular and gene therapies
  - Blood substitutes
- May be less information on design parameters, more need for flexibility
- Safety concerns
- Optimal design approaches?

# DATA MONITORING COMMITTEES

- Increasing use in industry trials
- Many different models
- Fundamental issues not widely understood
- FDA draft guidance on DMCs addressed basic principles
- Revised, "final" guidance informed by much thoughtful input
- Will have particular relevance for flexible designs, with changes motivated by interim data

# TRIAL DESIGN AND ANALYSIS

- Noninferiority trials
  - ICH E10 gives general principles for noninferiority trials but little specifics
  - Optimal approach for defining acceptable difference not yet defined
  - Active area of research in CBER
- Missing data
  - No "preferred" analytical approach
  - Need for continued research and discussion

# VACCINE SAFETY

- Concerns about vaccine safety arise regularly
- CBER maintains an intense post-market safety review program for new vaccines
- Early post-market experience reported in high-profile journals
- Enhancement of public confidence

# VACCINE SAFETY

- Annual meeting with CDC vaccine safety staff and vaccine manufacturers
- Availability of AE reports on web facilitate manufacturer's awareness of reports made directly to FDA
- Partnering with PhRMA on data mining initiative
- Use of health care databases to investigate rare adverse effects

# VACCINE SAFETY

- In some cases, small trials sufficient to establish vaccine efficacy
- Growing public interest in vaccine safety implies need for more safety data
- What is best way to evaluate safety of new vaccines?
  - Large simple trials (pre- or post-licensure)
  - Improved methods of post-market surveillance
  - Other approaches

# DATA MINING

- New tool to improve sensitivity of post-market safety surveillance
- Concern: false positives that could have nontrivial consequences
  - Multiplicity
  - Threshold for "signal"
- FDA-PhRMA working group formed to develop "best practices" for data mining
- CBER co-chairs subgroup for vaccines

# RISK ANALYSIS

- Decision-making often needed in absence of full information
- Modeling risks can help by showing potential influence of parameters whose values are unknown/uncertain
- Models can also be useful in identifying what additional data would be most valuable in reducing uncertainty

# RISK ANALYSIS

- Risk analysis/modeling in CBER has been used to help understand
  - Risks of vCJD and CJD transmission via blood and tissue products
  - Implications of widespread smallpox vaccination programs for blood supply
  - Possible impact of a low efficacy HIV vaccination

# STAFF TRAINING

- Difficult to make progress if staff unfamiliar with new concepts
- New reviewers often lack strong background in quantitative methods
- Training is critical
  - Clinical trials methods
  - Basic biostatistics
  - Data monitoring committees (new!)
  - Methods in risk analysis/communication (new!)

# COLLABORATIONS

- Progress in developing and adopting improved methods requires substantial communication among FDA, sister agencies, industry, academia
- Collaborations foster consistency within FDA and transparency to stakeholders
- CBER has many such collaborations in the area of quantitative methods
  - Workshops
  - Working groups

# COLLABORATIONS

- Annual conferences/workshops
  - FDA/Industry statistical workshop
  - FDA/PhRMA workshop
  - FDA/CDC and vaccine manufacturers
- Focused conferences/workshops
  - Bayesian methods in clinical trials
  - Adaptive/flexible designs
  - Data monitoring committees
- Working groups
  - Data mining in post-market surveillance

# COLLABORATIONS

- International Conference on Harmonization (ICH)
- Professional societies
  - Drug Information Association
  - International Society of Pharmacoepidemiology
  - American Statistical Association
  - International Biometric Society
  - Society for Clinical Trials
  - American Association for the Advancement of Science

# SUMMARY

- Quantitative methods are central to many critical path issues
- Quantitative methods will be needed to assess potential gains from new approaches
- CBER statisticians and epidemiologists are involved in many of the issues identified by stakeholders

# RECOMMENDATIONS?

- New collaborations
- Desirable staff training
- Outreach
- Application of new/emerging methods
- Methodological research
  - Design/analysis of trials
  - Post-marketing surveillance
  - Risk analysis
  - Risk communication in settings of substantial uncertainty